REMARKS

Status of the Claims

Claims 1-82 and 87-89 have been previously cancelled. Claims 83-86 and 90-94 were examined in the May 5, 2005 office action. Claim 90 has been amended in order to put it in better format. Accordingly, claims 83-86 and 90-94 will be pending upon entry of this amendment.

Rejections under 35 U.S.C. § 112- Written Description

The Examiner has maintained his rejections to claims 83-86 and 90-94 under 35 U.S.C. § 112, first paragraph, asserting that the claims lack written description in the disclosure of the application sufficient to reasonably convey to one of skill in the art that the inventor had possession of the invention at the time the invention was filed. Office Action at pages 2-6. Applicant respectfully traverses this rejection.

In the current Office Action, the Examiner has essentially ignored the Applicant's five pages of synopsis and analysis as to the current case law and PTO guidelines regarding the written description requirement and how it relates to the current claimed invention. Instead, the Examiner's position is that the Applicant's synopsis and analysis are speculation, and that his rejection is consistent with "the holdings of the Federal Circuit in addressing the written description requirement of CD40CR in parent application USSN 07/742,480. See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004)." The Examiner continues by stating that:

> [w]hile it is acknowledged that the claims of Noelle and the instant application differ, the present case concerns the identical issue of law based essentially on the same prior art/factual basis decided in Noelle. Given the facts are the same or nearly the same in the instant application as the facts in the preceding appeal of USSN 08/742,480, previously decided points of law should be followed unless overruled and the application of the law to the particular facts should be consistent from case to case.

Office Action at page 4. It is respectfully submitted that the Examiner's arguments are misplaced.

The written description requirement is a factual determination, thus, a case involving different claims cannot be relied upon to show that the present claims do not comply with the requirement. The present claims are method claims, that were not included in the interference that was the subject of the Noelle decision. These claims recite different limitations with respect to the antigen, limitations that the written description in the specification expressly supports. Moreover, CD40CR *is not recited in any of the current claims.* Instead, as fully shown below, the claims recite specific structural and functional features of the antigen that satisfy the requirement of a well-characterized antigen. The Examiner is charged with examining the pending claims, not claims that are not pending.

The Examiner contends that the facts of this case "are the same *or nearly the same*" as the facts in Noelle. It is respectfully submitted that the application of law from one case cannot automatically be applied to a case where the facts are *nearly the same.* Moreover, in this case, because the claims are different, the facts are not even "nearly the same." While clearly Noelle involved the parent of this application, to follow its holding as to a factual determination, without even considering the differences in the fact patterns of the two cases, is in error.

The Examiner states at page 2 of the Office Action that the Applicant is arguing sufficient written description of the claimed antigens is satisfied by the sufficient written description of the claimed antibodies. Later the Examiner asserts that the applicant has not disclosed "'a fully characterized antigen' as it reads on CD40CR antigen or the genus of CD40CR antigens encompassed by the claims." See Office Action at page 5. Applicant respectfully submits these findings are incorrect.

In the Amendment filed September 30, 2005, the Applicant showed fully that the claims cover and the specification describes the use of *an antibody that recognizes a well-characterized antigen.* The antigen is characterized by both structural and functional characteristics, which include: (1) the same molecular weight as a protein precipitated by a CD40 immunoglobulin

(CD40-Ig) fusion protein; (2) sequence and conformation that allow the binding with a soluble human CD40-Ig construction comprising the extracellular domain of a CD40 protein having the amino acid sequence of SEQ ID NO: 2 and an extracellular domain at the site of fusion having the amino acid sequence or SEQ ID NO:3; (3) presence on activated but not resting T-cells; and (4) pre-clearance by precipitation with soluble human CD40-Ig construct. Thus, in the present claims, the antigen is characterized by structural characteristics, cell distribution characteristics, and ligand-binding characteristics that are specifically set forth in the specification of the application, as shown in more detail below.

Antigen Physical Characteristics: The antigen has the same molecular weight as a protein bound by the Applicant's CD40-Ig construct, which has a ligand-binding domain fully characterized by the amino acid sequence (SEQ ID NO: 2). The antigen was and can be isolated and tested for molecular weight using methods identical to those employed in Example 1, page 28, lines 8-30 (Figure 4) and page 29, lines 13-17 (Figure 5b). Starting materials for the antigen can be cell membranes from activated helper T cells, prepared as described on page 21, lines 20-35; or as described in Example 2 (page 31, lines 20-31). As described on page 29, lines 16-17 and in Figure 5B, using plasma membranes from murine helper T-cells, CD40-Ig recognized a 39 kD protein.

Antigen Cell Distribution Characteristics: As described in Example 1, page 28, lines 8-30, the antigen is expressed on activated but not resting helper T-cells. This was shown in a binding assay where activated helper T-cells stained 56% positive with CD40-Ig but not with the control construct.

Antigen Ligand-Binding Characteristics: The antigen is pre-cleared by precipitation with CD40-Ig. See specification, page 29, lines 18-22. This shows that the antigen is a member of a specific binding pair with CD40-Ig.

In addition to fully describing characteristics that define the antigen, the claims cover and the specification supports characteristics of the antibody. While the description of the antigen itself is sufficient to meet the written description requirement, this further description of the

antibody bolsters the description of the subject matter of the claims. These additional unique characteristics of the antibody include both antigen binding and functional characteristics. The antibody blocks the specific binding of CD40-Ig to activated helper T-cells, which shows that the antibody and CD40 have overlapping binding epitopes on the antigen (page 29, lines 8-13) and the antibody has the functional characteristic of inhibiting T-cell activation of B-cells. This is supported by the specification at Example 1, page 28, line 25 to page 29, line 30 where it describes the MR1 antibody blocked B-cell activation while the control antibodies did not.

Thus, the current claims cover the use of a well-characterized antibody which recognizes a well-characterized antigen. The Examiner was incorrect in asserting that the Applicant was substituting the description of the former for the latter. On the contrary, the specification supports and describes both molecules and thus the claims are fully described in such a manner as to show that the Applicant was in possession of the subject matter of the invention at the time of filing.

The Examiner also asserts that the specification does not disclose a fully characterized antigen as it reads on human CD40CR antigen (Office Action, page 5) and criticizes the Example on page 31 of the specification asserting that it does not show binding studies with activated human T cells. *Id.* at page 3. Again Applicant respectfully submits this assertion is in error. The Example shows the binding of CD40-Ig to both Jurkat cell lines and HSB2 cell lines but not CEM, HPBALL and murine thymoma cell lines. The Applicant previously described both the Jurkat and HSB2 cell lines as activated helper T-cells. See specification, page 16, lines 6-8. Thus, one of skill in the art would have understood that the binding studies reported on page 31 of the specification would show the binding of CD40-Ig to human activated helper T cells, further showing that the human CD40 molecule is driving the binding of the CD40-Ig to human activated helper T cells.

The Examiner also asserts that the specification does not support a human or genus of CD40CR proteins because on page 30, paragraph 2, of the specification, the Applicant states that it is suspected that the 39 kD protein expressed on activated helper T cells but not resting T cells is "not one of these CD proteins." See Office Action at page 3. It is respectfully submitted that the

paragraph cited by the Examiner is discussing comparison of the murine 39 kD protein with *other types of CD proteins, not other species of CD40CR.* The full quotation from this paragraph, set forth below, illustrates this point.

> In an attempt to further characterize the 39 kD protein, cDNA encoding CD proteins in the MW range of 39 kD (CD 53, CD27 and CD69) were transiently transfected into COS cells and the cells were tested for CD40-Ig binding. None of the transfected COS cells expressed proteins that bound CD40-Ig. It is therefore suspected that the 39 kD protein is not one of these CD proteins.

Thus, the Examiner's assertions are incorrect and the current application provides specific examples of both murine and human CD40CR. However, this argument is somewhat moot because the current claims *do not cover or recite* CD40CR and more importantly, Applicant is not relying upon disclosure of species alone to support the claims. Instead, the Applicant relies upon the disclosure of relevant identifying characteristics such as those described in detail above, to establish the presence of sufficient written description. As the Examiner states on page 7 of the Office Action (emphasis added), this disclosure of identifying characteristics can alone show sufficient written description :

> The Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by .... disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled to known or disclosed correlation between function and structure, or by *a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus.*

Thus, not only does the present specification support the genus claims with examples of two species, but as also shown above and in the Applicant's prior amendment, the antigen is fully described by the disclosure of a combination of identifying characteristics sufficient to show the Applicant was in possession of the genus.

For all of the above reasons, it is clear that the specification adequately supports the pending claims 83-86 and 90-94. Reconsideration and withdrawal of this rejection is therefore earnestly requested.

Enablement Rejection under 35 U.S.C. § 112

Claims 83-86 and 90-94 stand rejected under 35 U.S.C. § 112 for lack of enablement. The Examiner contends that the present specification, while being enabled for "the protein specifically recognized by monoclonal antibody MR1 produced by the hybridoma having the ATCC Accession No. HB11048," does not reasonably provide enablement of any "antigen having the characteristics recited in instant claims 83-86 (a)-(c)." The Examiner further contends that there is not sufficient guidance and direction to the person of skill in the art to make and use the genus of CD40CR antigen, other than the mouse CD40CR antigen identified by the MR1 antibody. Furthermore, the Examiner relies upon the Noelle v. Lederman decision for his assertion that the claims are not enabled. This rejection is respectfully traversed.

The Examiner cites the decision in Noelle to support his assertion that the skilled artisan would have lacked a reasonable likelihood of success in isolating human CD40CR antigen given the disclosure of mouse CD40CR antigen. See Office Action at page 10. It is respectfully pointed out that the "reasonable likelihood of success" issue in the Noelle decision was in relation to the determination of whether an interference-in-fact existed between the claims of the Noelle application and those of the Lederman patent. The finding of the Board was not in any way related to enablement of the claims, nor was enablement ever discussed in the decision. Moreover, as also discussed above, the Noelle decision involved different claims with different terminology. The pending claims do not recite the term "CD40CR." Thus, it is respectfully submitted that the Noelle

decision, while related to the parent application of the application, should not be followed here. The factual and legal issues are too different for the Noelle decision to be binding or even considered in examining the current claims for enablement.

The Examiner also states that the disclosure of the limited example of a mouse CD40CR antigen does not support an entire genus of CD40CR antigen. See Office Action at page 8. It is respectfully submitted that the existence of working examples is only one of many factors to be considered when determining enablement, *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), and the existence of only one working example should not be fatal to enablement.

Moreover, Applicant submits that the claims do not recite the term "CD40CR" and that they are in essence reciting the use of a protein that recognized by CD40-Ig. CD40-Ig is functional and enabled for recognizing an antigen present on activated mouse and human T-cells and there are two working examples of CD40-Ig-bound antigens as well as the working example of the use of MR1 to isolate and characterize the mouse antigen. Additionally, the specification discloses and exemplifies how to make and use CD40-Ig (specification at page 22, line 23 to page 23, line 3; page 17, line 10 to page 19, line 20; and Examples, e.g., page 26, line 15 to page 29, line 30). Using the teachings of the specification, one of skill in the art can make CD40-Ig and use it to isolate antigens, characterize the antigens, produce antibodies that recognize the antigens, and use antibodies that recognize the antigens, without undue experimentation.

For all of the above reasons, it has been shown that the specification adequately enables the claims. Reconsideration and withdrawal of this rejection is earnestly requested.

Anticipation Rejection Under 35 U.S.C. § 102

The Examiner has also maintained his rejection to the claims as being anticipated under 35 U.S.C. § 102(a) by Lederman et al. (U.S. Patent No. 5,993,816, "Lederman"). See Office Action at page 10.

The Examiner contends that the Noelle Declaration under 37 C.F.R. 1.131 is deficient and thus, cannot be used to show prior invention. The first reason given for this alleged deficiency is that the Declaration does not aver that the invention was reduced to practice in the United States. Applicant respectfully submits this argument puts form over substance. While the Declaration does not expressly state that the reduction to practice took place in the United States, Dr. Noelle does aver that it was reduced to practice in his laboratory at Dartmouth University. It is respectfully submitted that it is common knowledge that Dartmouth University is in New Hampshire, in the United States. In fact, it is such common knowledge, one would not reasonably think that an additional statement that the reduction to practice took place in the United States would be necessary. Thus, it is clear from the Declaration that the reduction to practice took place in the United States.

Secondly, the Examiner contends that the Noelle Declaration does not support the breadth of the claimed methods. It is respectfully submitted that the Declaration which shows Dr Noelle's conception and reduction to practice of MR1 fully supports the claimed invention for the same reasons as discussed above. As shown in paragraph 11 of the Noelle Declaration, MR1 inherently possesses the properties of both the claimed antibody and the claimed antigen. Thus, it is respectfully submitted that the Noelle Declaration shows the claimed invention was conceived and reduced to practice in the United States prior to the earliest priority date of the Lederman patent, thus, the Lederman patent does not anticipate the claims under 35 U.S.C. § 102(e).

Even if one accepts the Examiner's arguments that the Noelle Declaration does not prove prior invention, the Examiner has not proven that Lederman anticipates the claimed methods. In arguing that Lederman anticipates the claimed invention, the Examiner contends that "[t]he same or nearly the same patients and endpoints are targeted by the same or nearly the same CD40L-specific antibodies." See Office Action at page 11. It is respectfully submitted that "nearly the same" is not the standard for anticipation, rather, every claim limitation must be "identically" found in the prior art reference. The Examiner has not shown this.

The Examiner contends that Lederman teaches methods of inhibiting humoral immune response and autoimmunity by 5c8 specific antibodies and that 5c8 antibody binds a protein that is the equivalent of the CD40CR antigen. However, there is no way to ascertain this from the Lederman patent. Thus, the general description of Lederman provides no teaching or suggestion of the claimed invention. Lederman does not teach the use of an antibody that binds an antigen that has the same molecular weight as a protein precipitated by CD40-Ig, *and* is pre-cleared by precipitation with CD40-Ig. Lederman also does not teach that this antibody blocks binding of CD40-Ig to the antigen. As stated above, in order for a reference to anticipate a claim, it must teach each and every aspect of the claims. The Lederman patent does not teach the methods of claims 83-86 and 90-94, thus it cannot anticipate the claims.

The Examiner further argues that the invention as claimed would be inherent properties of the methods taught in Lederman and that the reference need not set forth the substance of the invention. Applicant respectfully submits that this can only be true, if at all, for the specific 5c8 antibody.

For the reasons set forth above, it is earnestly requested that this rejection be reconsidered and withdrawn.

Obviousness Rejections under 35 U.S.C § 103

The Examiner has also maintained that the claims are obvious under 35 U.S.C. § 103 over Lederman in view of Armitage et al. (U.S. Patent No. 5,961,974 "Armitage"). Office Action at page 12.

It is respectfully submitted that the Noelle Declaration fully shows conception and reduction to practice of the claimed methods prior to the earliest date of the Lederman patent, removing the patent as a prior art reference.

Furthermore, there is no objective basis to combine Lederman and Armitage. The Lederman patent as filed does not mention CD40 or CD40CR. The knowledge that these molecules were disclosed in the Lederman patent came subsequent to its filing and subsequent to Applicant's effective filing date. There is also nothing in Armitage to suggest combining the two references because Armitage does not provide any more than a suggestion of an antibody, much less any functional characteristics of a such a hypothetical antibody that would suggest a correlation to Lederman's antibody.

Lastly, even if one were motivated to combine the two references, one of skill in the art would not arrive at the claimed invention. In order for the combination of the two references to render the claim obvious, they must teach or suggest each and every limitation of the claim, with a reasonable expectation of success. Applicant submits that is not the case here. Lederman combined with Armitage does not teach or suggest the use of an antibody that binds an antigen that has the same molecular weight as a protein precipitated by CD40-Ig, and is pre-cleared by precipitation with CD40-Ig. Nor do these reference teach or suggest that this antibody blocks binding of CD40-Ig to the antigen.

Thus, the Examiner's rejection for obviousness cannot be maintained. Lederman is not a proper prior art reference because the claimed invention was conceived and reduced to practice prior to the patent's earliest filing date. Even if considered prior art, there is no objective basis for combining Lederman with Armitage and even if combined, the two would not render the claimed invention obvious.

CONCLUSION

Applicant respectfully requests entry of the foregoing remarks in the file history of the application. As shown, the pending claims are patentable and this application is believed to be in immediate condition for allowance.

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Respectfully submitted,

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